IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF

CHENG ET AL.

APPLICATION NO: Division of Application Serial No. 09/812,960 Filed March 20, 2001

FILED: Herewith

FOR: SUBSTITUTED ACID DERIVATIVES USEFUL AS ANTIDIABETIC AND ANTIOBESITY AGENTS AND METHOD

Assistant Commissioner for Patents
Washington, D.C. 20231

PREEXAMINATION AMENDMENT

Sir:

Please amend the above-identified application to read as follows.

In the Specification:

Page 1, line 4, after "this" and before "is", please insert -- is a division of U.S. application Serial No. 09/812,960 filed March 20, 2001; which --

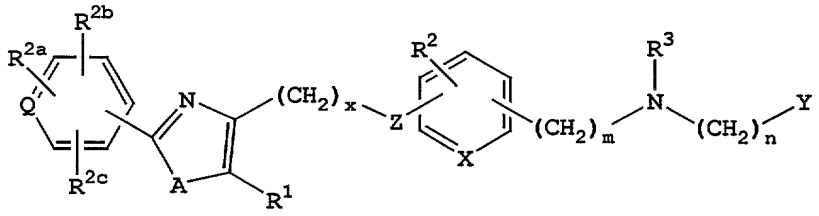
line 5, after "2000" and before "which", please insert -- , now abandoned, --.

In the Claims:

Please cancel Claims 6, 7, 8, 11, 12, 16, 18 to 32, 36, 38, 41 to 49 and 51 to 54.

Please amend Claims 1, 2, 10, 14, 15, 17, 34, 39, 40 and 50 to read as follows.

--1. (Amended) A compound which has the structure



wherein x is 1,2, 3 or 4; m is 1 or 2; n is 1 or 2;

Q is C or N;

A is O or S;

Z is O or a bond;

R^1 is H or lower alkyl;

X is N;

R^2 is H, alkyl, alkoxy, halogen, amino or substituted amino;

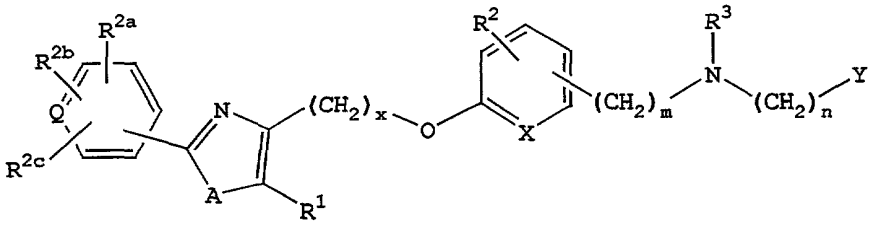
R^{2a}, R^{2b} and R^{2c} are the same or different and are selected from H, alkyl, alkoxy, halogen, amino or substituted amino;

R^3 is H, alkyl, arylalkyl, aryloxycarbonyl, alkyloxycarbonyl, alkynyloxycarbonyl, alkenyloxycarbonyl, arylcarbonyl, alkylcarbonyl, aryl, heteroaryl, alkyl(halo)aryloxycarbonyl, alkyloxy(halo)aryloxycarbonyl, cycloalkylaryloxycarbonyl, cycloalkyloxyaryloxycarbonyl, cycloheteroalkyl, heteroarylcarbonyl, heteroaryl-heteroarylalkyl, alkylcarbonylamino, arylcarbonylamino, heteroarylcarbonylamino, alkoxycarbonylamino, aryloxycarbonylamino, heteroaryloxycarbonylamino, heteroaryl-heteroarylcarbonyl, alkylsulfonyl, alkenylsulfonyl, heteroaryloxycarbonyl, cycloheteroalkyloxycarbonyl, heteroarylalkyl, aminocarbonyl, substituted aminocarbonyl, alkylaminocarbonyl, arylaminocarbonyl, heteroarylalkenyl, cycloheteroalkylheteroarylalkyl, hydroxyalkyl, alkoxy, alkoxyaryloxycarbonyl, arylalkyloxycarbonyl, alkylaryloxycarbonyl, arylheteroarylalkyl, arylalkylarylalkyl, aryloxyarylalkyl, alkynyloxycarbonyl, haloalkoxyaryloxycarbonyl, alkoxycarbonylaryloxycarbonyl, aryloxyaryloxycarbonyl, arylsulfinylarylcarbonyl, arylthioarylcarbonyl, arylalkenyloxycarbonyl, heteroaryloxyarylalkyl, aryloxyarylcarbonyl, aryloxyarylalkyloxycarbonyl, arylalkylcarbonyl, aryloxyalkyloxycarbonyl, arylalkylsulfonyl, arylthiocarbonyl, arylalkenylsulfonyl, heteroarylsulfonyl, arylsulfonyl, alkoxyarylalkyl, heteroarylalkoxycarbonyl, arylheteroarylalkyl, alkoxyarylcarbonyl, aryloxyheteroarylalkyl, heteroarylalkyloxyarylalkyl, arylarylalkyl, arylalkenylarylalkyl, arylalkoxyarylalkyl, arylcarbonylarylalkyl, alkylaryloxyarylalkyl, arylalkoxycarbonylheteroarylalkyl, heteroarylarylalkyl, arylcarbonylheteroarylalkyl, heteroaryloxyarylalkyl, arylalkenylheteroarylalkyl, arylaminoarylalkyl, aminocarbonylarylarylalkyl or polyhaloalkylaryloxycarbonyl;

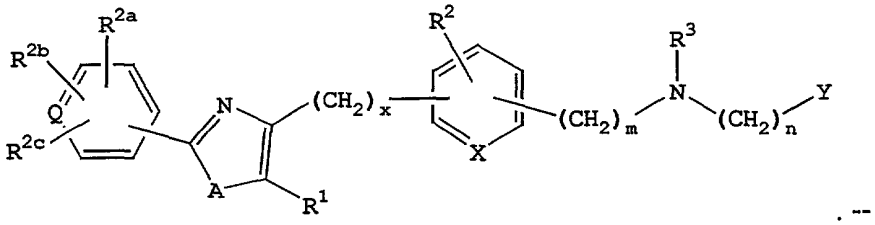
Y is CO_2R^4 where R^4 is H or alkyl, or a prodrug ester or Y is a C-linked 1-tetrazole, a phosphinic acid of the structure $P(O)(OR^{4a})R^5$ where R^{4a} is H or a prodrug ester, R^5 is alkyl or aryl or a phosphonic acid of the structure $P(O)(OR^{4a})_2$ where R^{4a} is H or a prodrug ester;

or stereoisomers thereof, prodrug esters thereof, and pharmaceutically acceptable salts thereof. --

--2. (Amended) The compound as defined in Claim 1 having the structure



or



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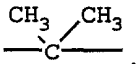
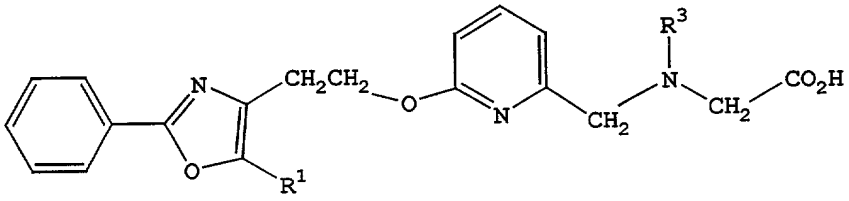
--10. (Amended) The compound as defined in Claim 1 wherein $(CH_2)_x$ is CH_2, $(CH_2)_2$, $(CH_2)_3$, or  , $(CH_2)_m$ is CH_2, or  where R_a is alkyl or alkenyl, $(CH_2)_n$ is CH_2, R^1 is lower alkyl, R^2 is H, R^{2a} is H, R^4 is H, X is CH, and R^3 is arylalkyloxycarbonyl, arylheteroarylalkyl, aryloxyarylalkyl, arylalkyl, aryloxycarbonyl, haloaryl-oxycarbonyl, alkoxyaryloxycarbonyl, alkylaryloxycarbonyl, aryloxyaryloxycarbonyl, heteroaryloxyarylalkyl, heteroaryloxycarbonyl, aryloxyarylcarbonyl, arylalkenyloxycarbonyl, cycloalkylaryloxycarbonyl, arylalkylarylcarbonyl, heteroaryl-heteroarylalkyl, cycloalkyloxyaryloxycarbonyl, heteroaryl-heteroarylcarbonyl, alkyloxyaryloxycarbonyl, arylalkylsulfonyl, arylalkenylsulfonyl, alkoxyarylalkyl, arylthiocarbonyl, cycloheteroalkylalkyloxycarbonyl, cycloheteroalkyloxycarbonyl, or polyhaloalkylaryloxycarbonyl, which may be optionally substituted. --

--14. (Amended) The compound as defined in Claim 1 having the structure



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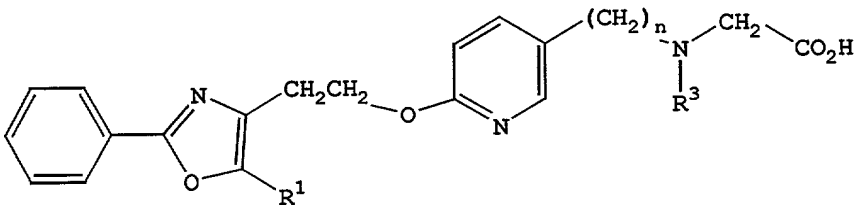
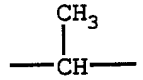
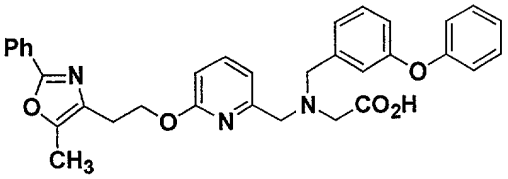
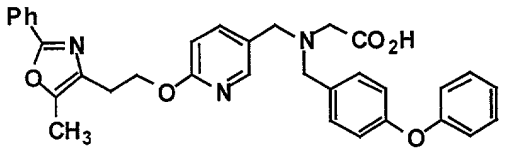
--15. (Amended) The compound as defined in Claim 1 having the structure

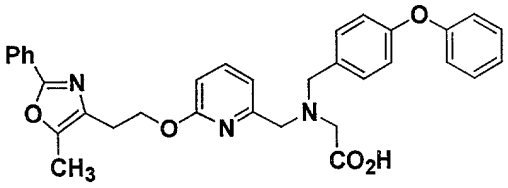


where $(CH_2)_n$ is CH_2 or  . --

--17. (Amended) The compound as defined in Claim 1 having the structure



,  or



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--34. (Amended) A method for lowering blood glucose levels or for treating diabetes or for treating a premalignant disease, an early malignant disease, a malignant disease, or a dysplastic disease, which comprises administering to a patient in need of treatment a therapeutically effective amount of a compound as defined in Claim 1. --

--39. (Amended) The combination as defined in Claim 37 wherein the antidiabetic agent is 1, 2, 3 or more of a biguanide, a sulfonyl urea, a glucosidase inhibitor, a PPARα agonist, a PPAR γ agonist, a PPAR α/γ dual agonist, an SGLT2 inhibitor, a DP4 inhibitor, an aP2 inhibitor, an insulin sensitizer, a glucagon-like peptide-I (GLP-I), insulin and/or a meglitinide; the anti-obesity agent is a beta 3 adrenergic agonist, a lipase inhibitor, a serotonin (and dopamine) reuptake inhibitor, a thyroid receptor agonist, an aP2 inhibitor and/or an anorectic agent; the lipid lowering agent is an MTP inhibitor, an HMG CoA reductase inhibitor, a squalene synthetase inhibitor, a fibric acid derivative, an upregulator of LDL receptor activity, a lipoxygenase inhibitor, or an ACAT inhibitor; the antihypertensive agent is an ACE inhibitor, angiotensin II receptor antagonist, NEP/ACE inhibitor, calcium channel blocker and/or β-adrenergic blocker. --

--40. (Amended) The combination as defined in Claim 39 wherein the antidiabetic agent is 1, 2, 3 or more of metformin, glyburide, glimepiride, glipyride, glipizide, chlorpropamide, gliclazide, acarbose, miglitol, pioglitazone, troglitazone, rosiglitazone, insulin, GI-262570, isaglitazone, JTT-501, NN-2344, L895645, YM-440, R-119702, AJ9677, repaglinide, nateglinide, KAD1129, AR-HO39242, GW-409544, KRP297, AC2993, LY315902, P32/98 and/or NVP-DPP-728A; the anti-obesity agent is orlistat, ATL-962, AJ9677, L750355, CP331648, sibutramine, topiramate, axokine, dexamphetamine, phentermine, phenylpropanolamine, and/or mazindol; the lipid lowering agent is pravastatin, lovastatin, simvastatin, atorvastatin, cerivastatin, fluvastatin, itavastatin, visastatin, fenofibrate, gemfibrozil, clofibrate, avasimibe, TS-962, MD-700, cholestagel, niacin and/or LY295427; the antihypertensive agent is an ACE inhibitor which is captopril, fosinopril, enalapril, lisinopril, quinapril, benazepril, fentiapril, ramipril or moexipril; an NEP/ACE inhibitor which is omapatrilat, [S[(R*,R*)]-hexahydro-6-[(2-mercapto-1-oxo-3-phenylpropyl)amino]-2,2-dimethyl-7-oxo-1H-azepine-1-acetic acid (gemopatrilat) or CGS 30440;

an angiotensin II receptor antagonist which is irbesartan, losartan or valsartan;

amlodipine besylate, prazosin HCl, verapamil, nifedipine, nadolol, propranolol, carvedilol, or clonidine HCl; the platelet aggregation inhibitor is aspirin, clopidogrel, ticlopidine, dipyridamole or ifetroban. --

--50. (Amended) A method for treating insulin resistance, hyperglycemia, hyperinsulinemia, or elevated blood levels of free fatty acids or glycerol, hyperlipidemia, obesity, Syndrome X, dysmetabolic syndrome, inflammation, diabetic complications, impaired glucose homeostasis, impaired glucose tolerance, hypertriglyceridemia, atherosclerosis, or for treating irritable bowel

syndrome, Crohn's disease, gastric ulceritis or osteroporosis, or psoriasis, which comprises administering to a mammalian species in need of treatment a therapeutically effective amount of a pharmaceutical combination as defined in Claim 37.--

REMARKS

Claims 1 to 5, 9, 10, 13 to 15, 17, 33 to 35, 37, 39, 40 and 50 are present.

The above claims cover compounds where X is N, that is, a non-elected invention in parent application Serial No. 09/812,960.

Claims 34 to 37 have been combined.

Claims 39, 42, 44 and 47 have been combined.

Claims 40, 43, 45, 48 and 49 have been combined.

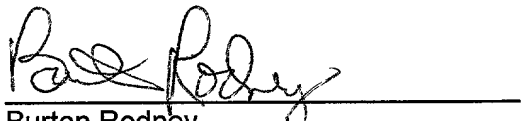
Claims 50 and 51 have been combined.

The addition of R^3 as polyhaloalkylaryloxycarbonyl in Claim 1 is based on original Claim 10, lines 29-30.

Basis for the compound added in Claim 17 is found on original page 346, next to last compound on left hand side.

It is believed that this application is in good form for examination.

Respectfully submitted,



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Attorney for Applicants
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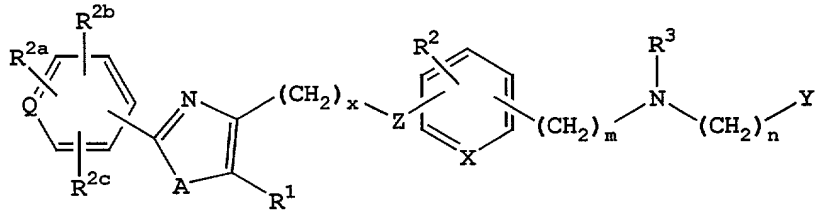
(609) 252-4336

Date: 2/22/02

VERSION WITH MARKINGS TO SHOW CHANGES MADE

--1. (Amended) A compound which has the structure



wherein x is 1,2, 3 or 4; m is 1 or 2; n is 1 or 2;

Q is C or N;

A is O or S;

Z is O or a bond;

R^1 is H or lower alkyl;

X is [CH or] N;

R^2 is H, alkyl, alkoxy, halogen, amino or substituted amino;

R^{2a}, R^{2b} and R^{2c} are the same or different and are selected from H, alkyl, alkoxy, halogen, amino or substituted amino;

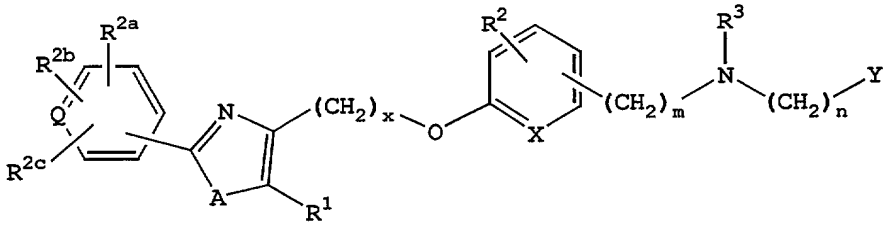
R^3 is H, alkyl, arylalkyl, aryloxycarbonyl, alkyloxycarbonyl, alkynyloxycarbonyl, alkenyloxycarbonyl, arylcarbonyl, alkylcarbonyl, aryl, heteroaryl, alkyl(halo)aryloxycarbonyl, alkyloxy(halo)aryloxycarbonyl, cycloalkylaryloxycarbonyl, cycloalkyloxyaryloxycarbonyl, cycloheteroalkyl, heteroarylcarbonyl, heteroaryl-heteroarylalkyl, alkylcarbonylamino, arylcarbonylamino, heteroarylcarbonylamino, alkoxycarbonylamino, aryloxycarbonylamino, heteroaryloxycarbonylamino, heteroaryl-heteroarylcarbonyl, alkylsulfonyl, alkenylsulfonyl, heteroaryloxycarbonyl, cycloheteroalkyloxycarbonyl, heteroarylalkyl, aminocarbonyl, substituted aminocarbonyl, alkylaminocarbonyl, arylaminocarbonyl, heteroarylalkenyl, cycloheteroalkylheteroarylalkyl, hydroxyalkyl, alkoxy, alkoxyaryloxycarbonyl, arylalkyloxycarbonyl, alkylaryloxycarbonyl, arylheteroarylalkyl, arylalkylarylalkyl, aryloxyarylalkyl, alkynyloxycarbonyl, haloalkoxyaryloxycarbonyl, alkoxycarbonylaryloxycarbonyl, aryloxyaryloxycarbonyl, arylsulfinylarylcarbonyl, arylthioarylcarbonyl,[alkoxycarbonylaryloxycarbonyl,] arylalkenyloxycarbonyl, heteroaryloxyarylalkyl, aryloxyarylcarbonyl, aryloxyarylalkyloxycarbonyl, [arylalkenyloxycarbonyl,] arylalkylcarbonyl, aryloxyalkyloxycarbonyl, arylalkylsulfonyl, arylthiocarbonyl, arylalkenylsulfonyl, heteroarylsulfonyl, [hateroarylsulfonyl,] arylsulfonyl,

alkoxyarylalkyl, heteroarylalkoxycarbonyl, arylheteroarylalkyl, alkoxyarylcarbonyl, aryloxyheteroarylalkyl, heteroarylalkyloxyarylalkyl, arylarylalkyl, arylalkenylarylalkyl, arylalkoxyarylalkyl, arylcarbonylarylalkyl, alkylaryloxyarylalkyl, arylalkoxycarbonylheteroarylalkyl, heteroarylarylalkyl, arylcarbonylheteroarylalkyl, heteroaryloxyarylalkyl, arylalkenylheteroarylalkyl, arylaminoarylalkyl, [or] aminocarbonylarylarylalkyl or polyhaloalkylaryloxycarbonyl;

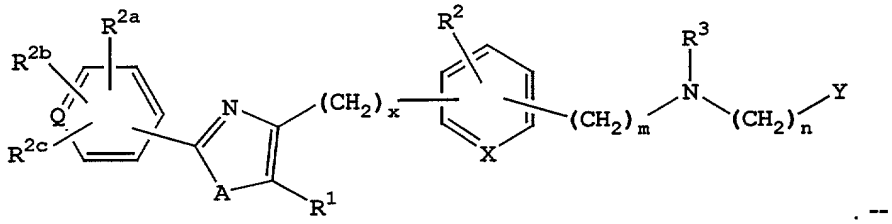
Y is CO_2R^4 [(]where R^4 is H or alkyl, or a prodrug ester[)] or Y is a C-linked 1-tetrazole, a phosphinic acid of the structure $P(O)(OR^{4a})R^5$[, (]where R^{4a} is H or a prodrug ester, R^5 is alkyl or aryl[)] or a phosphonic acid of the structure $P(O)(OR^{4a})_2$[, (]where R^{4a} is H or a prodrug ester[)];

or [including all] stereoisomers thereof, prodrug esters thereof, and pharmaceutically acceptable salts thereof[, with the proviso that where X is CH, A is O, Q is C, Z is O and Y is CO_2R^4, then R^3 is other than H or alkyl containing 1 to 5 carbons in the normal chain]. --

--2. (Amended) [A] The compound as defined in Claim 1 having the structure



or



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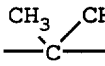
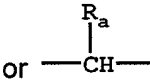
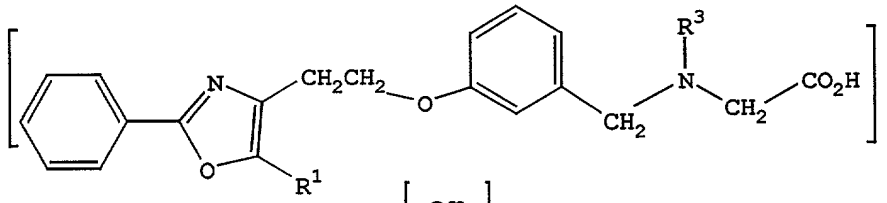
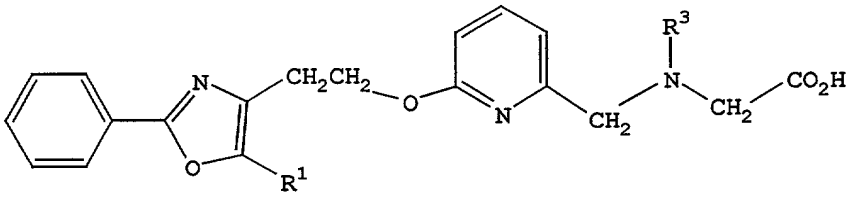
--10. (Amended) The compound as defined in Claim 1 wherein [R^{2a} is alkoxy or H,] $(CH_2)_x$ is CH_2, $(CH_2)_2$, $(CH_2)_3$, or  , $(CH_2)_m$ is CH_2, or  [(]where R_a is alkyl or alkenyl[)], $(CH_2)_n$ is CH_2, R^1 is lower alkyl, [preferably $-CH_3$,] R^2 is H, R^{2a} is H, R^4 is H, X is CH, and R^3 is arylalkyloxycarbonyl, arylheteroarylalkyl, aryloxyarylalkyl, arylalkyl, aryloxycarbonyl, haloaryl-oxycarbonyl, alkoxyaryloxycarbonyl, alkylaryloxycarbonyl, aryloxyaryloxycarbonyl,

heteroaryloxyarylalkyl, heteroaryloxycarbonyl, aryloxyarylcarbonyl, arylalkenyloxycarbonyl, cycloalkylaryloxycarbonyl, arylalkylarylcarbonyl, heteroaryl-heteroarylalkyl, cycloalkyloxyaryloxycarbonyl, heteroaryl-heteroarylcarbonyl, alkyloxyaryloxycarbonyl, arylalkylsulfonyl, arylalkenylsulfonyl, alkoxyarylalkyl, arylthiocarbonyl, cycloheteroalkylalkyloxycarbonyl, cycloheteroalkyloxycarbonyl, or polyhaloalkylaryloxycarbonyl, which may be optionally substituted. --

--14. (Amended) The compound as defined in Claim 1 having the structure



[or]



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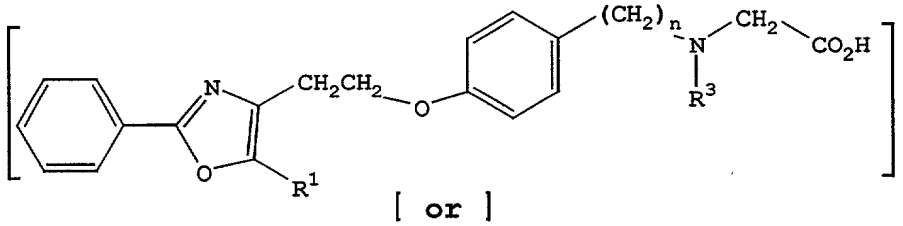
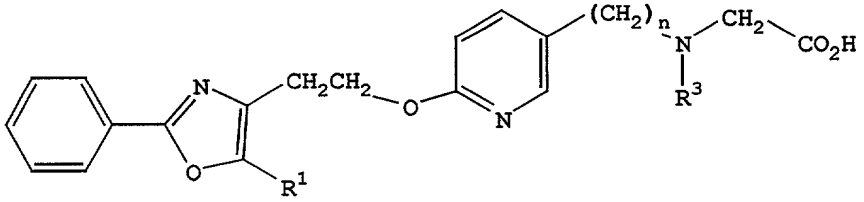
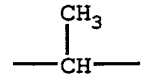
--15. (Amended) The compound as defined in Claim 1 having the structure

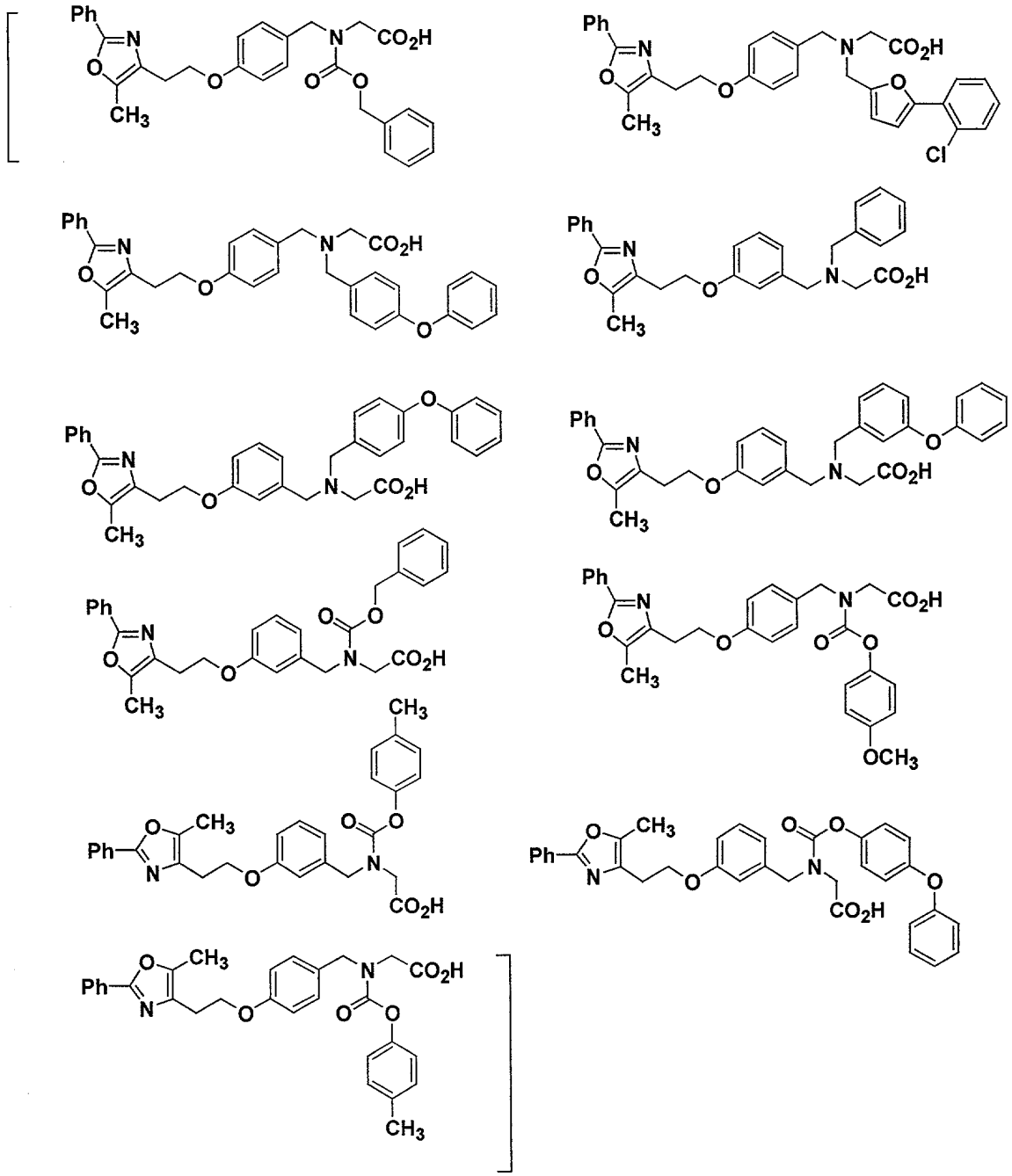


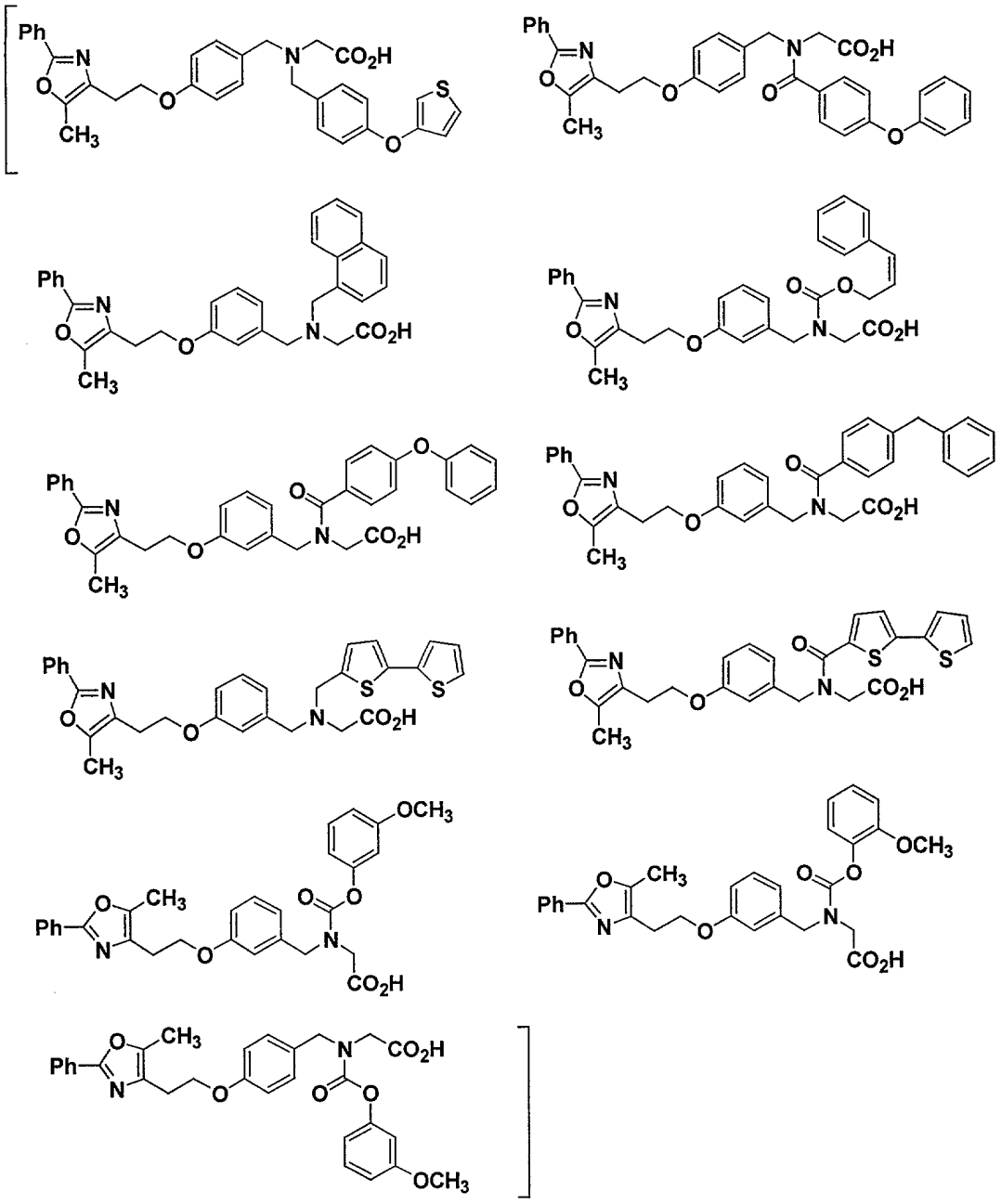
[or]

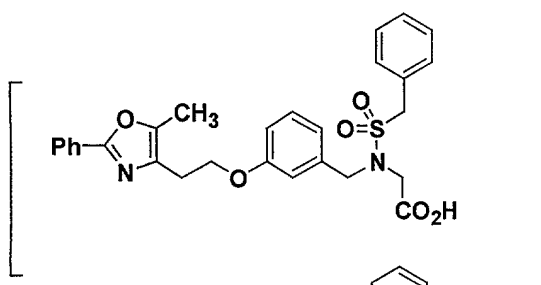


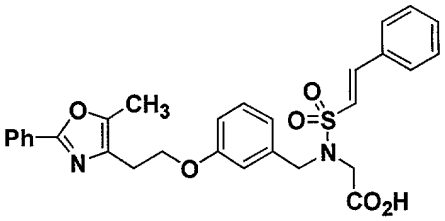
where $(CH_2)_n$ is CH_2 or  . --

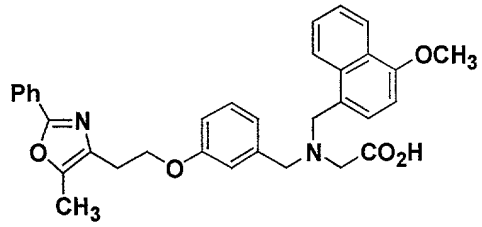
--17. (Amended) The compound as defined in Claim 1 having the structure

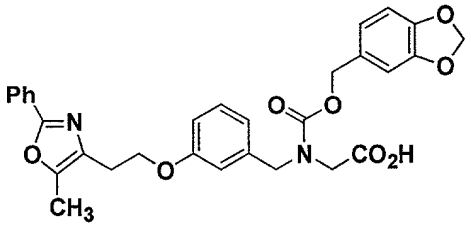


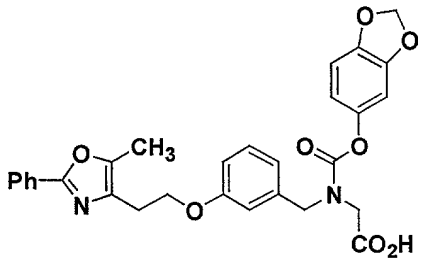


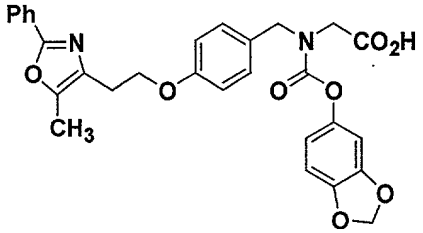


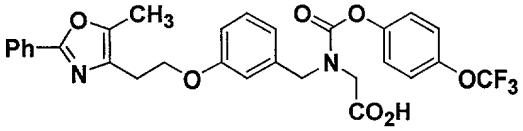


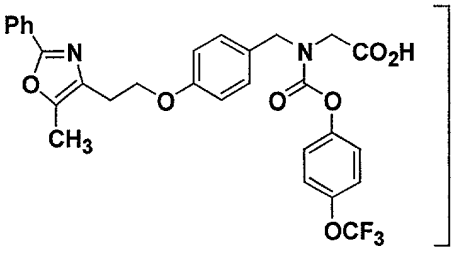


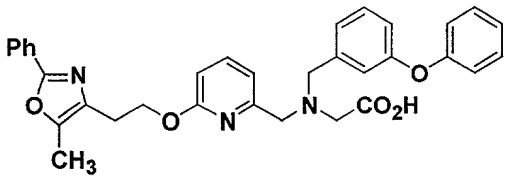


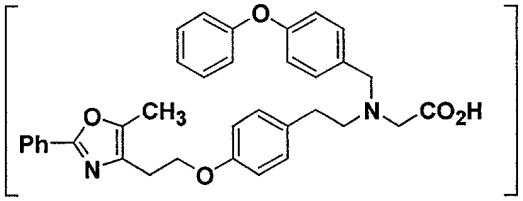


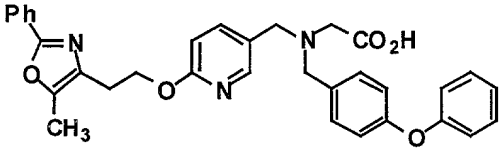












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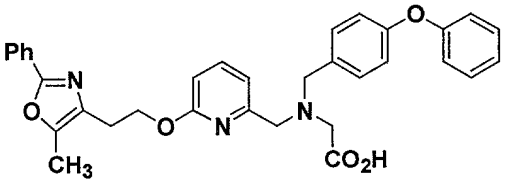

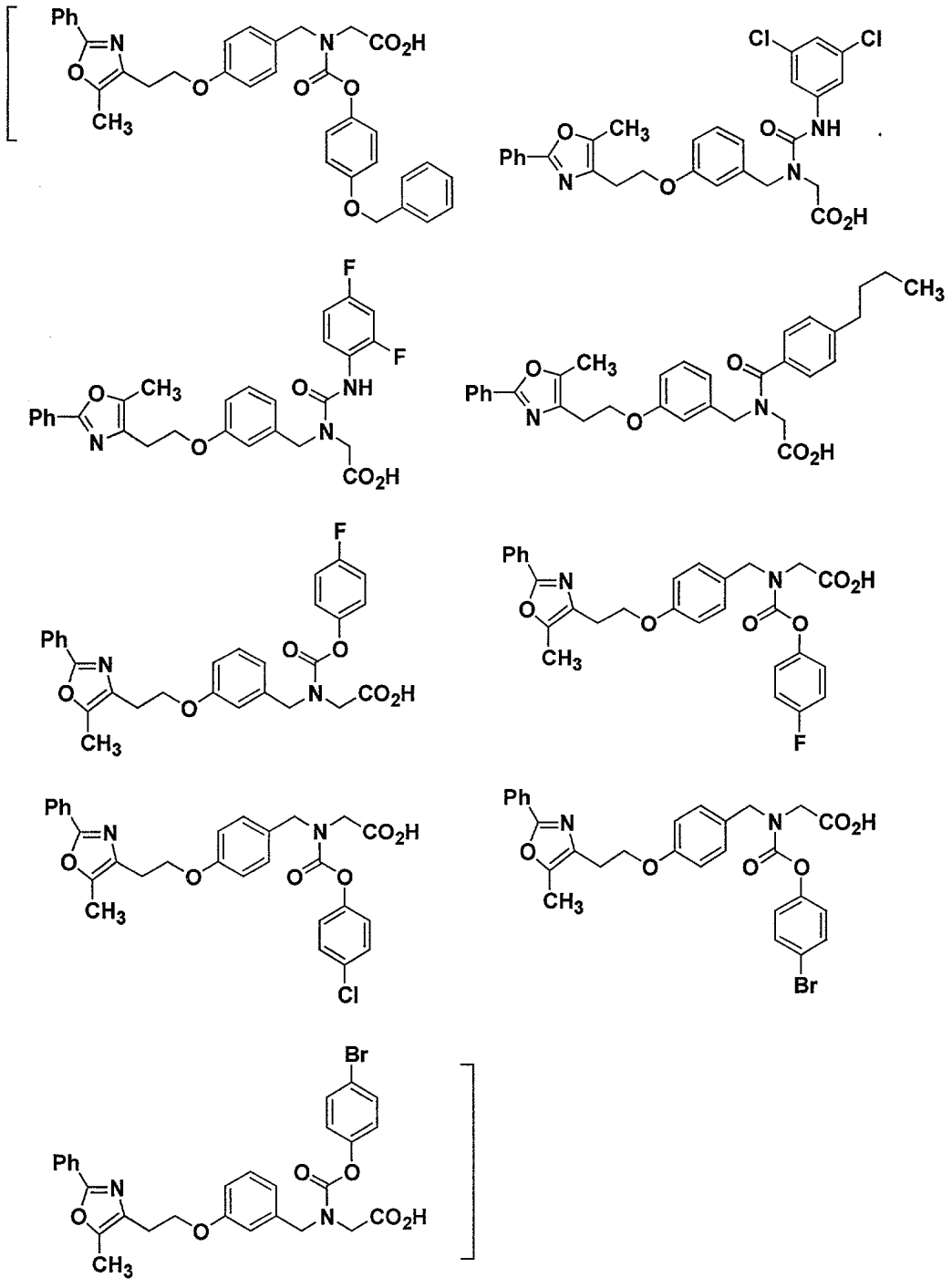

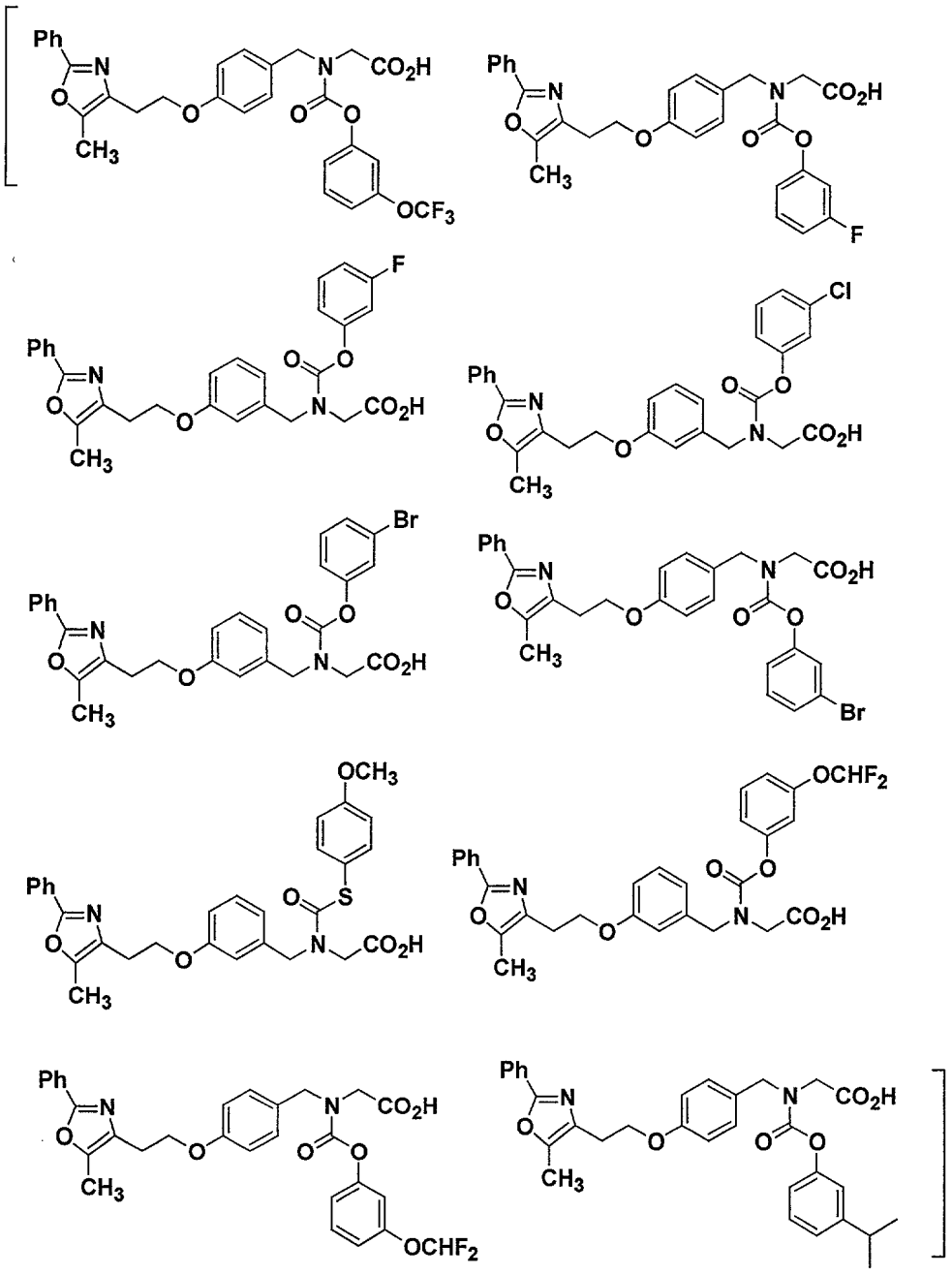

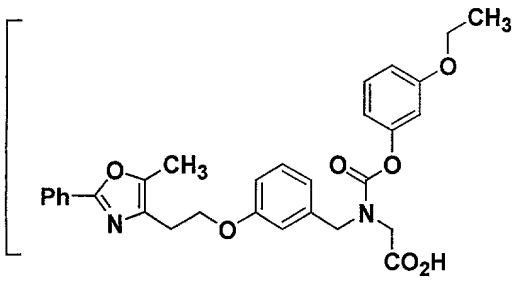

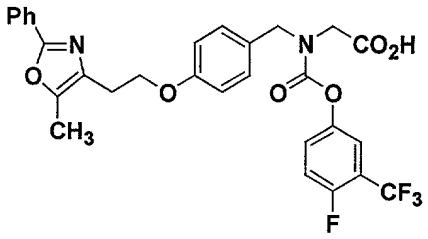

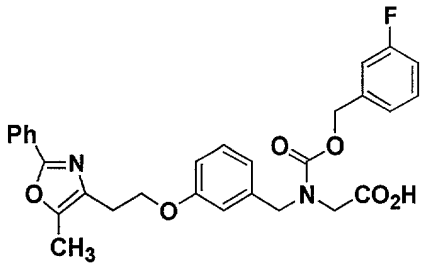

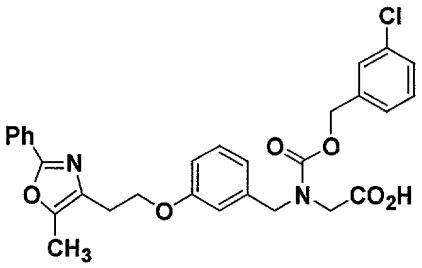

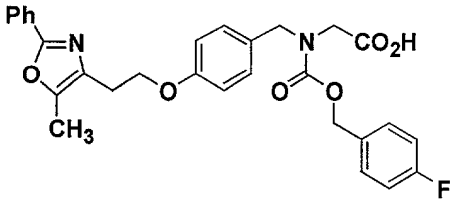

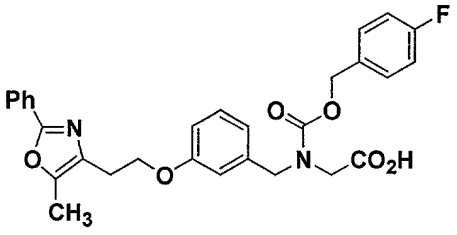

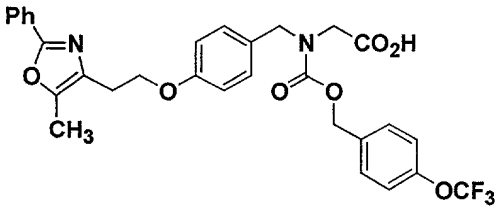

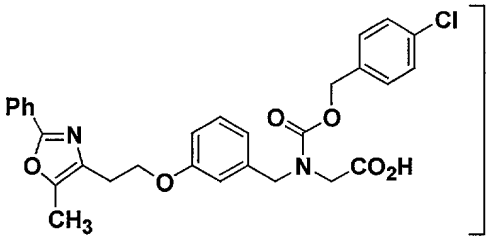

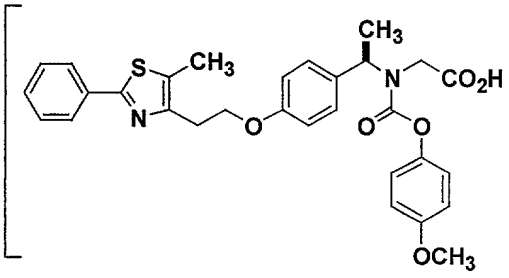

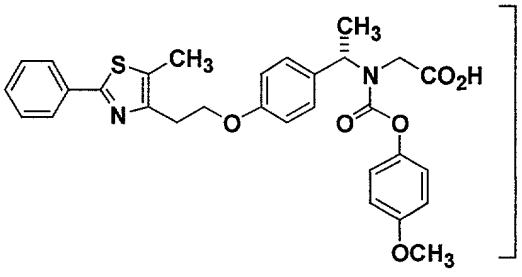

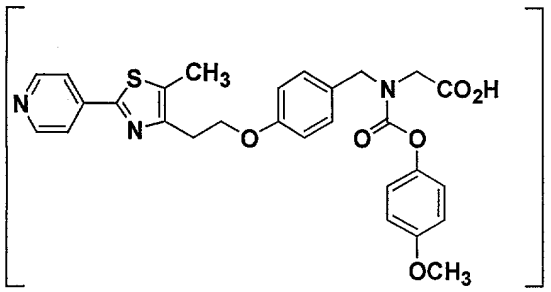

--34. (Amended) A method for lowering blood glucose levels or for treating diabetes or for treating a premalignant disease, an early malignant disease, a malignant disease, or a dysplastic disease, which comprises administering to a patient in need of treatment a therapeutically effective amount of a compound as defined in Claim 1. --

--39. (Amended) The combination as defined in Claim [38] 37 wherein the antidiabetic agent is 1, 2, 3 or more of a biguanide, a sulfonyl urea, a glucosidase inhibitor, a PPARα agonist, a PPAR γ agonist, a PPAR α/γ dual agonist, an SGLT2 inhibitor, a DP4 inhibitor, an aP2 inhibitor, an insulin sensitizer, a glucagon-like peptide-I (GLP-I), insulin and/or a meglitinide; the anti-obesity agent is a beta 3 adrenergic agonist, a lipase inhibitor, a serotonin (and dopamine) reuptake inhibitor, a thyroid receptor agonist, an aP2 inhibitor and/or an anorectic agent[,]; the lipid lowering agent is an MTP inhibitor, an HMG CoA reductase inhibitor, a squalene synthetase inhibitor, a fibric acid derivative, an upregulator of LDL receptor activity, a lipoxygenase inhibitor, or an ACAT inhibitor[,]; the antihypertensive agent is an ACE inhibitor, angiotensin II receptor antagonist, NEP/ACE inhibitor, calcium channel blocker and/or β-adrenergic blocker. --

--40. (Amended) The combination as defined in Claim 39 wherein the antidiabetic agent is 1, 2, 3 or more of metformin, glyburide, glimepiride, glipyride, glipizide, chlorpropamide, gliclazide, acarbose, miglitol, pioglitazone, troglitazone, rosiglitazone, insulin, GI-262570, isaglitazone, JTT-501, NN-2344, L895645, YM-440, R-119702, AJ9677, repaglinide, nateglinide, KAD1129, AR-HO39242, GW-409544, KRP297, AC2993, LY315902, P32/98 and/or NVP-DPP-728A[,]; the anti-obesity agent is orlistat, ATL-962, AJ9677, L750355, CP331648, sibutramine, topiramate, axokine, dexamphetamine, phentermine, phenylpropanolamine, and/or mazindol[,]; the lipid lowering agent is pravastatin, lovastatin, simvastatin, atorvastatin, cerivastatin, fluvastatin, itavastatin, visastatin, fenofibrate, gemfibrozil, clofibrate, avasimibe, TS-962, MD-700, cholestagel, niacin and/or

LY295427[,]; the antihypertensive agent is an ACE inhibitor which is captopril, fosinopril, enalapril, lisinopril, quinapril, benazepril, fentiapril, ramipril or moexipril; an NEP/ACE inhibitor which is omapatrilat, [S[(R*,R*)]-hexahydro-6-[(2-mercapto-1-oxo-3-phenylpropyl)amino]-2,2-dimethyl-7-oxo-1H-azepine-1-acetic acid (gemopatrilat) or CGS 30440;

an angiotensin II receptor antagonist which is irbesartan, losartan or valsartan; amlodipine besylate, prazosin HCl, verapamil, nifedipine, nadolol, propranolol, carvedilol, or clonidine HCl, the platelet aggregation inhibitor is aspirin, clopidogrel, ticlopidine, dipyridamole or ifetroban. --

--50. (Amended) A method for treating insulin resistance, hyperglycemia, hyperinsulinemia, or elevated blood levels of free fatty acids or glycerol, hyperlipidemia, obesity, Syndrome X, dysmetabolic syndrome, inflammation, diabetic complications, impaired glucose homeostasis, impaired glucose tolerance, hypertriglyceridemia, atherosclerosis, or for treating irritable bowel syndrome, Crohn's disease, gastric ulceritis or osteroporosis, or psoriasis which comprises administering to a mammalian species in need of treatment a therapeutically effective amount of a pharmaceutical combination as defined in Claim [43] 37.--